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10/591,045	08/29/2006	Johannes Auer	22388	7458

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EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,045	AUER ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 12/23/08 have been fully considered but they are not persuasive.

Claims 5-6 have been added. Claims 1-6 are under consideration by the examiner.

Applicant is advised that the amendment filed 12/23/08 is not fully compliant with 37 CFR 1.121. Not all changes to the claims were properly marked. See for example, claim 1 where "of SEQ ID NO: 3" was added but the insertion was not indicated by underlining. Applicant is advised to review all amendments carefully to avoid receiving a Notice of Non-Compliant Amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids and methods of producing HGF fragments as set forth below, does not reasonably provide enablement for all nucleic acids and methods embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is directed to "a nucleic acid of SEQ ID NO: 3 wherein least one of the codons of amino acids selected from the group consisting of codons at positions 3, 5 and 6 is CGT." First of all, it appears that a word has been omitted and that the claim should recite "wherein at least one." However, the claim is directed to any subfragment of SEQ ID NO: 3. That is, the minimal sequence required by the claim appears to be twelve nucleotides for codons 3-6 of SEQ ID NO: 3. A specific embodiment embraced by the claims would be "CGTAAACGTCGT."

Claim 5 is directed to a nucleic acid encoding an N-terminal fragment of SEQ ID NO: 2 wherein at least one of the codons at positions 2, 4 and 5 is CGT. However, the claim is directed to any N-terminal fragment of SEQ ID NO: 2. That is, the minimal sequence required by the claim appears to be twelve nucleotides for amino acids 2-6 of SEQ ID NO: 2. A specific embodiment embraced by the claims would be "CGTAAACGTCGT."

The specification does not tell how to use these small nucleic acid fragments nor the small protein fragments produced by the methods of claims 3-4. The encoded protein fragments would not have been expected to have any biological activity. The specification exemplifies producing an NK4 protein using a particular nucleic acid. (See example 1 at page 6.) There are no examples nor disclosure of different fragments commensurate with the scope of the claims that would have been expected to have been biologically active. With respect to claim 3 the recitation of "NK polypeptide" as disclosed on page 2 includes any N-terminal fragment. Claim 3 as written is not considered to be limited to NK polypeptides as described on page 3 (consisting of at least amino acids 32-207 and having activity in a scatter assay according to Example 4). It is further noted that claim 3 contains a variety of typographical errors including "denatured from" in line 5 and "condos" in line 6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stahl et al. in view of Fuglsang, Olivares-Trejo et al., and Jeh et al.

Stahl et al. discloses high-level recombinant expression of HGF NK1 and NK2 in E. coli (see abstract). On page 765, right column, fourth paragraph NK1 and NK2 are disclosed to accumulate to about 10-20% of the total protein (see also page 2, lines 14 and 15 of the present application). The inclusion bodies are solubilized and the proteins renatured. Stahl et al. does not disclose substituting at least one of the codons at positions 33, 35 and 36 (in claim 5), or the three codons simultaneously (in claim 6) by CGT.

Fuglsang discloses the preferred codon usage in Escherichia coli. Table 2 discloses that

the most optimal codon for Arg in E. coli is CGT (it has the most negative correlation of RSCU with Nc(AA), and the most positive correlation of RSCU with CAI).

Olivares-Trejo et al. discloses that an increase in the synthesis of a particular protein in E. coli is observed when the rare arginine codons AGA and AGG at positions 3 and 4 are changed to CGT (see abstract, and page 1046, right column, first paragraph), which are exactly the same changes as proposed in claims 5-6 of the present application.

Jeh et al. also discloses an improved production method of flounder growth hormone (fGH) in E. coli. In this method the first 15 codons of the wild type fGH were randomly altered to search for the most optimal expression of fGH. The increase was from a low expression level of 6% to a 25% of the total cell protein (see paragraph bridging left and right columns in page 188). The highly expressing clones included as the optimal Arg encoding codon, CGT (the same referred to in claims 5-6 of the present application) as shown in figure 3 of Jeh et al.

The HGF natural codons at position 33 is AGG, and at positions 35 and 36 is AGA. (Numbering according to Genbank M73239 and corresponding to amino acid positions 2, 4, and 5 of claims 5-6 and amino acid positions 3, 5, and 6 of claims 1-4.) Both AGG and AGA are shown in Table 2 of Fuglsang not to be optimal codons in E. coli. Thus, the skilled person would have been motivated to substitute the naturally occurring codons at positions 2, 4, and 5 (or 3, 5, and 6) by the most optimal codon for Arg, which is CGT, in order to improve expression of the α-chain of HGF or an N-terminal fragment thereof. It would have been obvious to produce the HGF recombinantly using a codon optimized nucleic acid sequence to optimize production. The combined teachings of Stahl et al., Fuglsang, Olivares-Trejo et al., and Jeh et al. would have

motivated the skilled person to substitute more preferred arginine codons for the less preferred naturally occurring codons.

SEQ ID NO: 2 is a 463 amino acid sequence for the α-chain of HGF. The protein of Stahl et al. constitutes an "N-terminal fragment of SEQ ID NO: 2."

SEQ ID NO: 3 is a 1350 nt sequence encoding NK4 having Met SerArg instead of Gln Arg at the N-terminal. It includes two stop codons at the 3' end and the codons CGT for amino acids 3, 5, and 6. The nucleic acid used by Stahl et al. comprises "a nucleic acid of SEQ ID NO: 3." That is, it contains a subsequence of SEQ ID NO: 3. The claims do not require the entirety of SEQ ID NO: 3 nor any particular subsequence of SEQ ID NO: 3 beyond the three codons recited in the claims. The methionine at amino acid position 1 of SEQ ID NO: 4 is not required. The substitution of serine for glutamine as seen in amino acid position 2 of SEQ ID NO: 4 is not required.

With respect to the arguments presented with respect to the rejection of claims 1-4 in the prior Office action, applicant is improperly arguing the references individually and not for what they collectively teach. Codon bias and using codon optimized sequences with alternate codons for the same amino acid to improve recombinant production would have been well known to those of ordinary skill in the art at the time of the invention. The art recognized the particular codons altered by applicant as being rare for the host cell (E. coli) used by applicant. Applicant has not established any unexpected results for any nucleic acid embraced by claims 1-6.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa